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(54) Title: SOLID-PHASE NUCLEOPHILIC FLUORINATION

(57) Abstract: The present invention relates to novel solid-phase processes for the production of radiolabelled tracers, in particular for the production of ^{18}F-labelled compounds which may be suitable for use as Positron Emission Tomography (PET) radiotracers. The invention also comprises radiopharmaceutical kits using these novel processes.

SOLID-PHASE NUCLEOPHILIC FLUORINATION

The present invention relates to novel solid-phase processes for the production of radiolabelled tracers, in particular for the production of ^{18}F-labelled compounds which may be suitable for use as Positron Emission Tomography (PET) radiotracers. The invention also comprises radiopharmaceutical kits using these novel processes.

The favoured radioisotope for PET, ^{18}F, has a relatively short half-life of 110 minutes. ^{18}F-labelled tracers for PET therefore have to be synthesised and purified as rapidly as possible, and ideally within one hour of clinical use. Standard synthetic methods for introducing fluorine-18 are relatively slow and require post-reaction purification (for example, by HPLC) which means that it is difficult to obtain the ^{18}F-labelled tracer for clinical use in good radiochemical yield. There is also a need for automation to protect the operator from radiation exposure. Many radiofluorinations are complicated procedures and it is necessary to simplify them to facilitate automation.

The present invention provides solid-phase processes for producing ^{18}F-labelled tracers quickly and with high specific activity yet avoiding time-consuming purification steps, such that the resultant ^{18}F-labelled tracer is suitable for use in PET. The solid-phase methods also lend themselves to automation with advantages of ease of production and greater throughput. The invention also comprises radiopharmaceutical kits which use such processes and thus provide the radiopharmacist or clinician with a convenient means of preparing an ^{18}F-labelled tracer.

In a general aspect, the invention provides a process for the production of an ^{18}F-labelled tracer which comprises treatment of a resin-bound precursor of formula (I)

SOLID SUPPORT-LINKER- X -TRACER (I)

with $^{18}F^-$ to produce the labelled tracer of formula (II)

^{18}F-TRACER (II)

As the ^{18}F-labelled tracer of formula (II) is removed from the solid-phase into solution, all unreacted precursor remains bound to the resin and can be separated by simple filtration, thus obviating the need for complicated purification, for example by HPLC. The ^{18}F-labelled tracer of formula (II) may be cleaned up by removal of excess F^-, for example by ion-exchange chromatography and/or by removal of any organic solvent. The resultant ^{18}F-labelled tracer of formula (II) may then be further made-up into an aqueous formulation for clinical use.

Examples of tracers which may be ^{18}F-labelled in the manner of the invention include 2-fluoro-2-deoxy-D-glucose (FDG), 6-fluoro-L-DOPA (FDOPA), 3'-deoxy-3'-fluorothymidine (FLT), 2-(1,1-dicyanopropen-2-yl)-6-(2-fluoroethyl)-methylamino)-naphthalene (FDDNP), 2-, 5-, and 6-fluoro (2(S)-azetinylmethoxy)pyridines, N-succinimidyl-4-[18F]fluorobenzoate ([18F]-SFB) and peptides. In preferred aspects of the invention, the tracer produced is selected from FDG, FDOPA, FLT, and FDDNP, and is most preferably FDG or FDOPA.

In the compounds of formula (I), X is a group which promotes nucleophilic substitution at a specific site on the attached TRACER. Examples of X include $-SO_2O-$ as in formula (Ia) below, I^+ as in formula (Id) below, or $-N(C_{1-6}alkyl)_2^+-$ as in formula (If) below.

In a further aspect, the invention provides a process for the production of an ^{18}F-labelled tracer which comprises treatment of a resin-bound precursor of formula (Ia)

SOLID SUPPORT-LINKER-SO_2-O -TRACER (Ia)

with $^{18}F^-$ to produce the labelled tracer of formula (II)

^{18}F-TRACER (II)

followed by optionally

(i) removal of excess $^{18}F^-$, for example by ion-exchange chromatography; and/or

(ii) removal of any protecting groups; and/or

(iii) removal of organic solvent; and/or

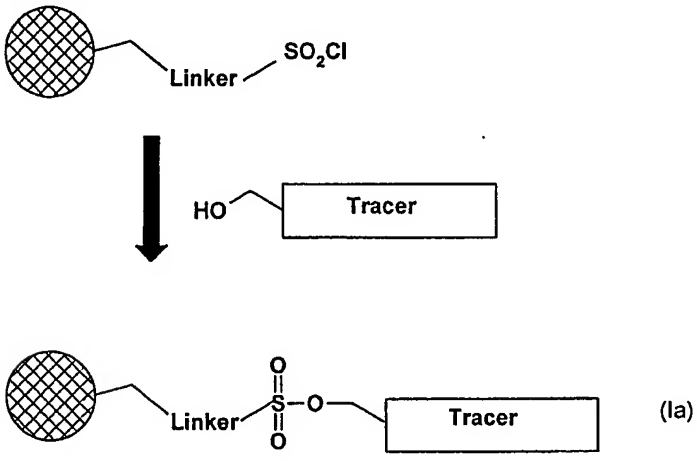
(iv) formulation of the resultant compound of formula (II) as an aqueous solution.

In the compound of formula (Ia), the TRACER is suitably FDG, FLT, FDDNP or a precursor thereof in which one or more functional groups have been protected, or an activated precursor of FDOPA. Most suitably, the TRACER in the compound of formula (Ia) is FDG or a precursor thereof.

As shown in Scheme 1, the compound of formula (Ia) may be conveniently prepared from any sulphonic acid functionalised commercially available resin, such as Merrifield Resin, NovaSyn® TG Bromo Resin, (Bromomethyl)phenoxymethyl polystyrene, or Wang Resin which may be reacted with a chlorinating agent to give the corresponding sulphonyl chloride resin. This may be carried out by treating the resin with, for example, phosphorus pentachloride, phosphorus trichloride, oxalyl chloride, or thionyl chloride, in an appropriate inert solvent such as dichloromethane, chloroform, or acetonitrile, and heating at elevated temperature for a period of time. The excess reagent may then be removed from the resin by washing with further portions of the inert solvent. The sulphonyl chloride resin may then be reacted with the alcohol analogue of the tracer to produce the resin-bound precursor of formula (Ia). This may be carried out by treating the resin with a solution of the alcohol in an inert solvent such as chloroform, dichloromethane, acetonitrile, or tetrahydrofuran

containing a non-nucleophilic soluble base such as sodium hydride or a trialkylamine, for example triethylamine or diisopropylethylamine. The reaction may be carried out at a temperature of 10 to 80°C, optimally at ambient temperature for a period of from around 1 to 24 hours. The excess alcohol and base may then be removed from the solid support by washing with further portions of an inert solvent such as chloroform, dichloromethane, or tetrahydrofuran.

Scheme 1

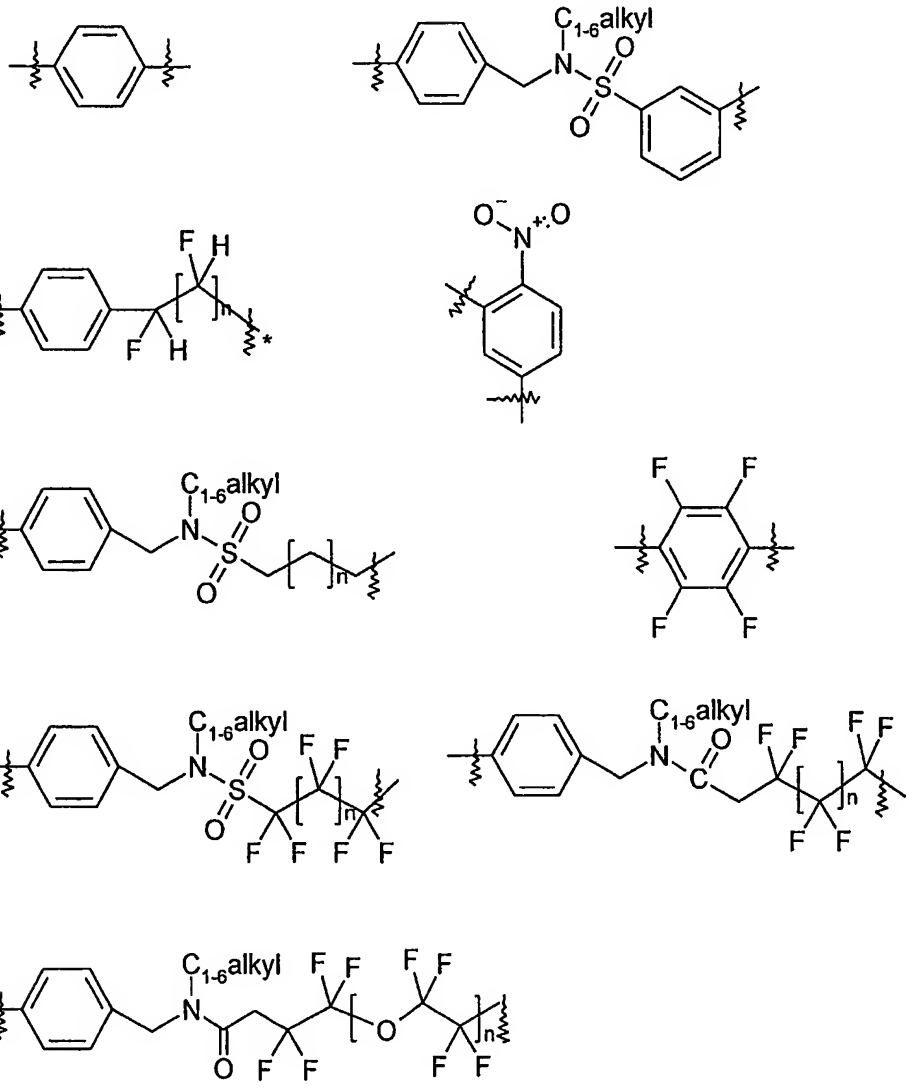


(Ia)

In the compounds of formulae (I) and (Ia) and in the following more specific aspects of the invention, the "SOLID SUPPORT" may be any suitable solid-phase support which is insoluble in any solvents to be used in the process but to which the LINKER and/or TRACER can be covalently bound. Examples of suitable SOLID SUPPORT include polymers such as polystyrene (which may be block grafted, for example with polyethylene glycol), polyacrylamide, or polypropylene or glass or silicon coated with such a polymer. The solid support may be in the form of small discrete particles such as beads or pins, or as a coating on the inner surface of a cartridge or on a microfabricated vessel.

In the compounds of formulae (I) and (Ia) and in the following more specific aspects of the invention, the "LINKER" may be any suitable organic group which

serves to space the reactive site sufficiently from the solid support structure so as to maximise reactivity. Suitably, the LINKER comprises zero to four aryl groups (suitably phenyl) and/or a C_{1-6} alkyl or C_{1-6}haloalkyl (suitably C_{1-6} fluoroalkyl), and optionally one to four additional functional groups such as amide or sulphonamide groups. Examples of such linkers are well known to those skilled in the art of solid-phase chemistry, but include:

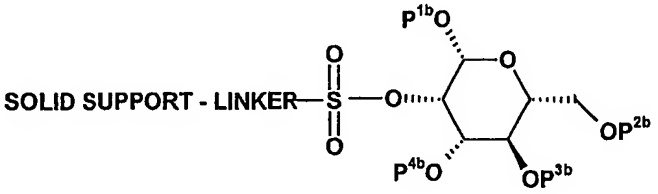


wherein at each occurrence, n is an integer of 0 to 3.

evaporation at elevated temperature *in vacuo* or by passing a stream of inert gas such as nitrogen or argon over the solution.

Before use of the ^{18}F-labelled tracer, it may be appropriate to formulate it, for example as an aqueous solution by dissolving the ^{18}F-labelled tracer in sterile isotonic saline which may contain up to 10% of a suitable organic solvent such as ethanol, or a suitable buffered solution such as phosphate buffer. Other additives may be added such as ascorbic acid to reduce radiolysis.

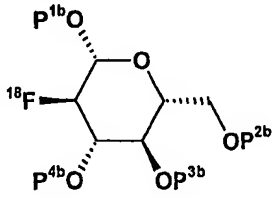
The present invention provides, in a further aspect, a process for the production of 2-^{18}F-fluoro-2-deoxy-D-glucose (^{18}F-FDG) which comprises treatment of a solid support-bound precursor of formula (Ib):



(Ib)

wherein P^{1b}, P^{2b}, P^{3b}, and P^{4b} are each independently hydrogen or a protecting group;

with $^{18}F^-$ to produce the labelled tracer of formula (IIb)



(IIb)

wherein P^{1b}, P^{2b}, P^{3b}, and P^{4b} are each independently hydrogen or a protecting group;

optionally followed by

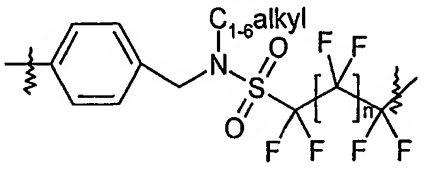
(i) removal of excess $^{18}F^-$, for example by ion-exchange chromatography; and/or

(ii) removal of the protecting groups; and/or

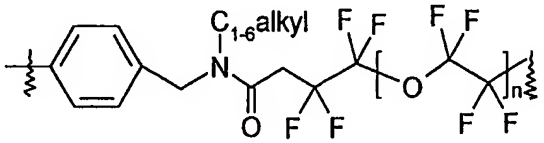
(iii) removal of organic solvent; and/or

(iv) formulation of the resultant compound of formula (IIb) as an aqueous solution.

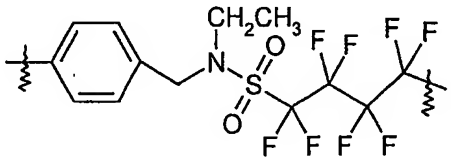
In the compound of formula (Ib) the LINKER is preferably



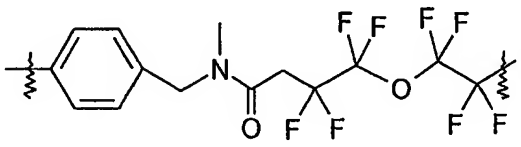
or



wherein n is 0 to 3, and is more preferably



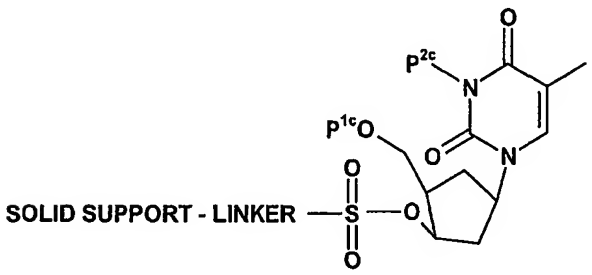
or



and the SOLID SUPPORT is suitably a polystyrene resin.

Removal of any protecting groups from the compound of formula (IIb) may be effected by standard methods as referred to above. In a preferred embodiment of this aspect of the invention, the sugar hydroxyl groups are protected as esters, suitably C_{1-6} alkanoic esters, preferably as acetate esters, or as ethers, preferably C_{1-6}alkoxy methyl ethers, or acetals. Ester, acetal, or ether protecting groups may be conveniently removed by hydrolysis, for example in the presence of acid or base. Such deprotection may be effected on using solid supported acid or base catalysts that render the need for post deprotection neutralisation unnecessary

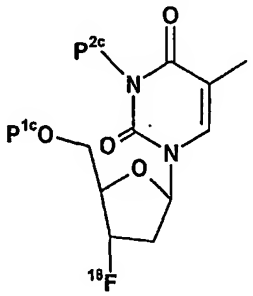
The present invention provides in a further aspect, a process for the production of 3'-deoxy-3'-^{18}F-fluorothymidine (^{18}F-FLT) which comprises treatment of a solid support-bound precursor of formula (Ic):



(Ic)

wherein P^{1c} and P^{2c} are each independently hydrogen or a protecting group;

with $^{18}F^-$ to produce the labelled tracer of formula (IIc)



(IIc)

wherein P^{1c} and P^{2c} are each independently hydrogen or a protecting group;

optionally followed by

(i) removal of excess $^{18}F^-$, for example by ion-exchange chromatography; and/or

(ii) removal of the protecting groups; and/or

(ii) removal of organic solvent; and/or

(iii) formulation of the resultant compound of formula (IIc) as an aqueous solution.

In this aspect of the invention, the amine and hydroxyl functional groups in the thymidine precursor are suitably protected using standard methods as referred to